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ALSTON & BIRD LLP
PIONEER HI-BRED INTERNATIONAL, INC.
BANK OF AMERICA PLAZA
101 SOUTH TYRON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

| EXAMINER |
|---|
| KUBELIK, ANNE R |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1638 | 17 |

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/829,481 | PRESNAIL ET AL. | |
| | Examin r | Art Unit | |
| | Anne R. Kubelik | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8,12-16,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12-16,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *with the application* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. In light of Applicant's having sent the references referred to in the response filed 21 February 2003 but their not being in the case, and in light of Applicant's sending the references on 30 May 2003, the finality of the action of 20 May 2003 is been withdrawn.

2. Claims 1-8, 12-16 and 22-23 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 112*

4. Claims 1-8, 12-16 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 21 November 2002, as applied to claims 1-8, 12-16 and 22. Applicant's arguments filed 21 February 2003 and 30 May 2003 have been fully considered but they are not persuasive.

Applicant urges that the specification teaches defensin-encoding nucleic acids from *Scolopendra canidens* and *Argiope*, as well as *Vaejovis carolinianus*. Applicant urges that SEQ ID NO:4 is a cationic peptide and contains all the conserved cysteine residues found in insect defensins, as shown in Appendix A. Applicant also urges that SEQ ID NO:4 has a high degree of similarity with the Arthropod defensin consensus sequence, as shown in Appendix B. Applicant cites Bulet et al, who state that insect defensins have cysteine stabilized alpha helices

and Cho et al, who show an alignment of insect and scorpion defensins (2/21/03 response pg 3-5 and 5/30/03 response pg 7-9).

This is not found persuasive. It is not clear in Appendix A what the sequences in the lower portion are. Appendix B contains little textual explanation - for example, what is the significance of the capital letters vs the lower case letters in the alignment? What do the plus signs mean? Thus, Appendix A and B could not be evaluated. Thus, these alignments could not be compared the alignments of Bulet et al and Cho et al. Explanation of Appendix A and B may provide the evidence needed to overcome this part of the rejection.

Applicant urges that the USPTO accepts sequence homology as a basis for establishing utility and that this rejection is typically made under both 35 USC 101 and 35 USC 112. Applicant urges that the Utility guidelines make it clear that sequence homology is sufficient to establish utility and that working examples are not required for establishment of utility. Applicant urges that nucleic acids encoding defensins have a well-established utility, comparable to ligase in the Utility Guideline Training Materials Example 10 (2/21/03 response pg 6-7 and 5/30/03 response pg 10-11).

This is not found persuasive. This is a rejection made under 35 USC 112, so Applicant's arguments regarding the Utility Training Guidelines are moot. It is noted that considerations for evaluating the claims under 35 USC 112 are different than those made for evaluating the claims under 35 USC 101.

Applicant urges that the prior art discusses defensin gene families from a wide array of organisms and they have similarities from 58% to 95%. Applicant urges that assays performed on proteins with these properties have confirmed that they have defensin activity. Applicant

cites Bulet et al, Cho et al, White et al, and Broekaert et al to state that defensins have similarities of 58-95%. Applicant cites Lamberty et al, Thevissen et al, and Terras et al to state that assays of proteins that have defensin properties have shown that they have defensin activity. Applicant urges that one of skill in the art would accept that SEQ ID NO:4 functions as a defensin (2/21/03 response pg 7-8 and 5/30/03 response pg 11-12).

This is not found persuasive because. Broekaert et al, Terras et al and Thevissen et al are directed toward a radish anti-fungal peptide and present no comparisons to Arthropod defensins. The peptide isolated by Lamberty et al unexpectedly lacks antibacterial activity (pg 9325, right column, paragraph 3). Applicant is invited to submit a Declaration showing the protein of SEQ ID NO:4 has antibacterial properties.

Applicant urges that there are several critical differences between the instant inventions and Pang et al and Barton et al, cited in the prior Office action. Applicant urges that these studies sought to control large insect predators, while defensins protect against pathogens, including Gram-positive bacteria. Applicant cites Boman et al, White et al, Cho et al, Bulet et al and Hetru et al to state that defensins have broad spectrum activities. Applicant urges that while the defensins of the instant invention may also provide protection against insect pathogens, some defensins protect against fungal and bacterial infection; Applicant cites Terras et al and Brockaert et al, to state that plants expressing defensins inhibit pathogens. Applicant urges that the fact that the Pang and Barton studies could not control insects using non-defensin proteins is irrelevant and numerous studies have demonstrated the efficacy of defensins against a wide array of bacterial and fungal pathogens (2/21/03 response pg 8-10 and 5/30/03 response pg 12-14).

This is not found persuasive. Boman et al, White et al, Cho et al, Bulet et al and Hetru et al do not address the unpredictability as discussed in the prior Office action. The unpredictability is that defensive proteins, when expressed in plants, unexpectedly do not work. Boman et al, White et al, Cho et al, Bulet et al and Hetru et al do not transgenically express the defensins in plants.

The proteins described by Brockaert et al were not transgenically expressed in plants. The protein described by Terras et al was not transgenically expressed in a plant - the antifungal assays were done with endogenously expressed protein - and thus has no relevance to the portion of the enablement rejection directed to unpredictability of expression of these proteins in plants.

Applicant's arguments with respect to Pang et al and Barton et al are off topic. These references were discussed in the rejection because they show that when small proteins are expressed in plants they may unexpectedly not work, even though the isolated protein was quite effective. In the case of Pang et al, this occurred because the protein was not correctly processed (pg 170, right column). The specification does not overcome this unpredictability by showing that SEQ ID NO:3 can be effectively expressed in a plant to produce a functional protein.

Applicant urges that one of skill in the art, using the guidance presented in the specification, could make and use the claimed invention, and urges that the specification provides guidance for determining percent identity of sequences. Applicant also urges that claim 1 specifies that the protein has defensin activity and thus encompasses functional variants. Applicant states that Terras et al, Oh et al, Thevissen et al (1996), and Thevissen et al (1999) and Lamberty et al teach defensin assays. Applicant urges that thus guidance is provided as to which region of SEQ ID NO:4 can be altered and that the claimed sequences can vary by structural

parameters and are required to retain defensin activity (2/21/03 response pg 10-11 and 5/30/03 response pg 14-15).

This is not found persuasive. None of Terras et al, Oh et al, Thevissen et al (1996), and Thevissen et al (1999) and Lamberty et al teach modification of defensins; the rejection was not a lack of enablement for methods of assaying defensins. Applicant did not point to guidance in the specification for which regions of SEQ ID NO:4 can be altered; guidance for calculating percent identity is not the same as guidance for making amino acid substitutions that result in a protein with a specified activity. Which amino acids of SEQ ID NO:4 are essential for defensin activity and which can be altered, and to what other amino acids?

Applicant urges that undue experimentation would not required to make and use the claimed invention, and cites *In re Wands* and *In re Jackson*, which states that experimentation is permissible. Applicant urges that shuffling to make and assay a number of sequences is taught in US Patent 5,837,458. Applicant also cites Minshull et al and Christains et al. Applicants states that *In re Wands* only considered the experimentation required to identify one or few monoclonal antibodies with the required affinity and *Johns Hopkins vs Cellpro* states that only one mode of making the claimed invention need to enabled. Applicant urges that guidance for making a nucleic acid with the applicable limitation of the claims and assaying the encoded protein is provided in the specification (2/21/03 response pg 11-13 and 5/30/03 response pg 15-17).

This is not found persuasive because the specification does not teach the critical amino acids of SEQ ID NO:4. The specification teaches no nucleic acids that encode proteins with 90% identity to SEQ ID NO:4, and it is not clear that SEQ ID NO:4 is a defensin, as discussed

above. None of the cited references could be considered because they were not sent, even in the response filed 30 May 2003.

Applicant is invited to submit a Declaration showing the protein of SEQ ID NO:4 has antibacterial properties and that plants transformed with a nucleic acid encoding it are more resistant to pathogens than nontransformed plants. Applicant is also invited to submit a Declaration showing that nucleic acids that encode proteins with 90% identity to SEQ ID NO:4 and made using the guidance presented in the specification are antibacterial proteins.

5. Claims 1-8, 12-16 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 21 November 2002, as applied to claims 1-8, 12-16 and 22. Applicant's arguments filed 21 February 2003 and 30 May 2003 have been fully considered but they are not persuasive.

Applicant urges that claim 1 requires that the protein has defensin activity and that it have 90% identity to SEQ ID NO:4. Applicant urges that recitation of at least 90% sequence identity is a very predictable structure. Applicant urges that all that is required is disclosure of a representative number of the claimed sequences, not individual support for each species of a claimed genus. Applicant urges that a genus of DNAs may be claimed by recitation of structural features common to the genus, and functional characteristics may be relied on; Applicant urges that claim 1 recites the functional characteristics of the claimed genus (2/21/03 response pg 13-14 and 5/30/03 response pg 17-18).

This is not found persuasive. It is agreed that the structure of nucleic acids that encode proteins with 90% identity to SEQ ID NO:4 is very predictable. However, the structure of nucleic acids that encode proteins with 90% identity to SEQ ID NO:4 and that encode a protein with defensin activity is not. The specification does not describe the structural features (*i.e.*, sequence) of even one such nucleic acid.

Applicant urges that Example 14 of the Written Description Guidelines states that claim to a protein with 95% sequence identity to a sequence identifier and that recites the reaction catalyzed by the protein meets the written description requirement; thus, Applicant urges the instant claims also meet the Written Description Guidelines (2/21/03 response pg 14-15 and 5/30/03 response pg 18-19).

This is not found persuasive because the claims are drawn to nucleic acids that encode proteins with **90%** identity to SEQ ID NO:4; thus, they do not fit the scenario in Example 14 of the Written Description Guidelines.

Applicant urges that *Eli Lilly* and *Amgen* do not apply to the present situation because structural and functional definitions are provided (response pg 15-16 and 5/30/03 response pg 19-20).

This is not found persuasive because the specification does not describe the structural features (*i.e.*, sequence) of nucleic acids that encode proteins with 90% identity to SEQ ID NO:4.

6. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

Claim 22 lacks antecedent basis for the limitation "said cells" in line 4.

7. Claims 1-8, 12-16 and 22 are free of the prior art, given the failure of the prior art to teach or suggest an isolated nucleic acid encoding a protein with at least 80% identity to SEQ ID NO:4.

***Conclusion***

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
June 24, 2003

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600